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Biochemical markers of bone turnover

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A consensus group from the International Osteoporosis Foundation (IOF) recommends the use of bone turnover markers for monitoring anti-resorptive agents and prediction of fracture risk in postmenopausal osteoporosis.[1] In 2006, the Canadian Consensus Conference on Osteoporosis indicated that bone turnover markers can be used to rapidly assess adherence and effectiveness of pharmacological interventions, stating that Bone Mineral Density (BMD) should not be viewed as the only indicator for management success because therapy may or may not be associated with significant increases in BMD.[2]

Bone turnover, also called bone remodelling, is a dynamic, lifelong process in which old bone tissue is replaced by new bone tissue. Normally comprising five phases[1] *(Figure 1)*, this process mainly occurs in the adult skeleton to maintain bone mass and involves the coupling of bone formation and bone resorption.

Under normal conditions, the resorption phase takes approximately 10 days, which is then followed by a formation phase that can last for up to 3 months. In a typical situation, bone resorption and formation are tightly coupled to each other, so that the amount of bone removed is always equal to the amount of newly formed bone. This balance is regulated through the action of various systemic hormones (e.g. PTH, vitamin D and other steroid hormones) and local mediators (e.g. cytokines and growth factors).

In contrast, ageing, metabolic bone diseases, states of increased or decreased mobility, therapeutic interventions and many other conditions are characterised by more or less pronounced imbalances in bone turnover.

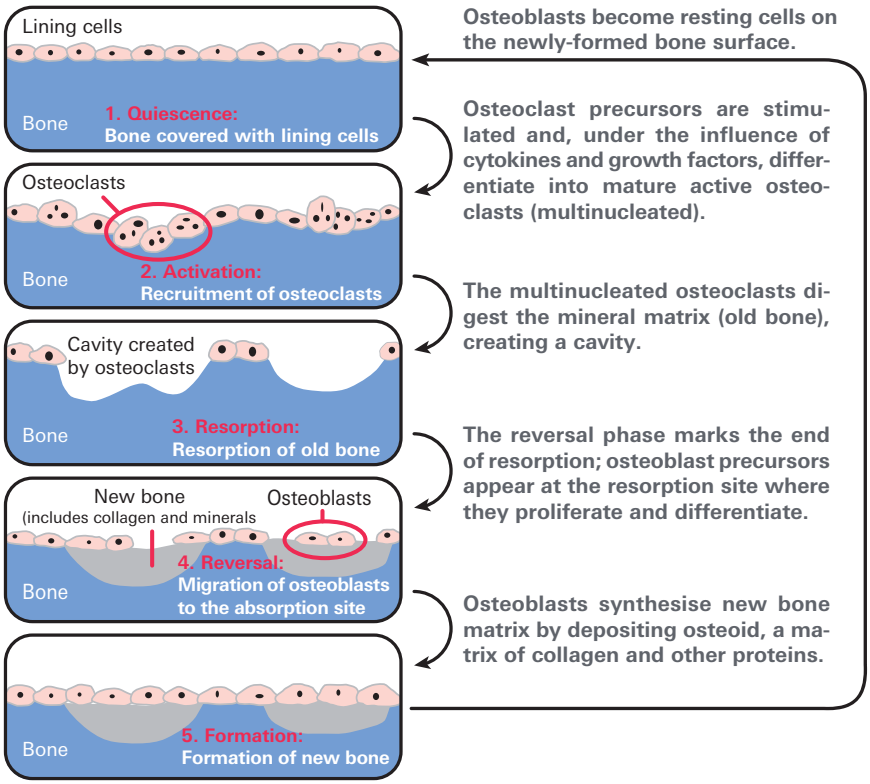

Figure 1: Normal bone remodelling cycle

Biochemical bone markers

Bone markers are products derived from the bone remodelling process. During this process, compounds are released either from bone or from the cells involved in the bone remodelling process (osteoblasts and osteoclasts). Depending on their involvement in the bone remodelling process, they are categorised into bone formation or resorption markers.

Bone resorption markers

Bone resorption markers are all related to osteoclast resorption of the matrix: dissolution of the mineralised matrix (tartrate-resistant acid phosphatase) and degradation of the protein matrix, specifically type I collagen. A great advance has been the development of serum assays, which exclude the need for creatinine measurements used to correct for volume differences in urine samples.

Tartrate-resistant acid phosphatase (TRAcP) is synthesised by osteoclasts, released into the resorption lacunae and presumed to help in the dissolution of the mineral matrix. Two forms of TRAcP circulate in human blood: TRAcP 5a derived from macrophages and dendritic cells, and TRAcP 5b derived from osteoclasts. The 5a isoform makes up approximately 90 % of circulating TRAcP. Recent data have demonstrated the utility of TRAcP 5b as a marker of osteoclast activity and TRAcP 5a as a marker of inflammatory conditions.[13, 14]

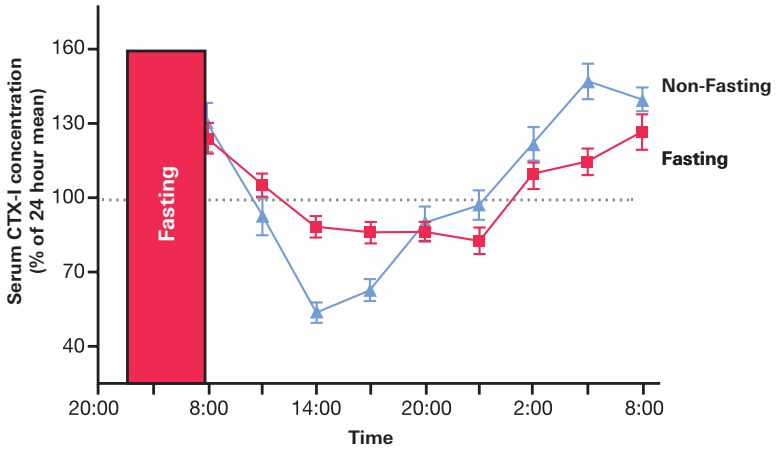

Figure 2: Circadian variation in serum CTX-I concentration in 11 premenopausal women measured with Serum CrossLaps® (CTX-I) ELISA
Christgau, S. Clin. Chem. 46 (3), 431, 2000

Cross-linked telopeptides – C-telopeptide (CTX) and N-telopeptide (NTX). In the process of bone resorption, amino- and carboxy-terminal fragments of collagen are released with cross-links attached. These fragments with attached cross-links are called telopeptides. N-telopeptides (NTX) and C-telopeptides (CTX) are secreted into blood and urine. Determination of CTX and NTX in serum is recommended for monitoring the efficacy of antiresorptive therapy (e. g. bisphosphonates or hormone replacement therapy – HRT) in osteoporosis or other bone diseases.[3–10]

Pyridinoline (PYD) and deoxypyridinoline (DPD). PYD are cross-linking amino acids that strengthen the collagen fibrils in the extracellular matrix. They are found in the main fibril-forming collagens (types I, II, and III) of many tissues. PYD is found in cartilage, bone, ligaments and vessels, whereas DPD is found in bone and dentin only.[11, 12]

Bone formation markers

These markers reflect different aspects of osteoblast function and of bone formation. Bone formation markers are related to the deposition of the protein matrix during new bone formation (markers: osteocalcin (OC) and propeptides of type I collagen (PICP and PINP)) and the calcification of the matrix (marker: bone-specific alkaline phosphatase (BAP)).

Procollagen type I propeptides. An important step in the bone formation process is the synthesis of type I collagen, which is the major organic component in bone matrix. During collagen synthesis, the amino (N-)terminal propeptide (PINP) and the carboxy (C-)terminal propeptide (PICP) are released from both the amino- and the carboxyterminal parts of the procollagen molecule.[15] These propeptides are secreted into the circulating blood. PINP is a particularly useful marker for monitoring the efficacy of osteoporosis therapy with anabolic agents, but it is also one of the best bone turnover markers for monitoring the efficacy of anti-resorptive therapy.[16–18]

Bone-specific alkaline phosphatase. BAP is synthesised by osteoblasts and is presumed to be involved in the calcification of the matrix. The half-life of BAP is 1–2 days, making it less sensitive to circadian variation than other markers with a shorter half-life. Changes in BAP levels have been shown to be useful markers in patients undergoing therapy for metabolic bone disorders.[19–22] BAP is one of several isoenzymes of alkaline phosphatase (AP), originating from different tissues. Usually, about half the AP in the serum of adults comes from bone.

Osteocalcin is the most abundant noncollagenous protein in the bone matrix. It is released by osteoblasts during bone formation and embedded into the bone matrix. Serum osteocalcin is elevated in diseases characterised by increased bone turnover such as osteoporosis, hyperparathyroidism and Paget's disease and supressed in conditions associated with low bone turnover such as hypoparathyroidism and growth hormone deficiency.[21, 22] It has been shown that immunoassays measuring both intact (amino acids 1–49) and large N-MID fragments (amino acids 1–43, resulting from proteolytic cleavage after blood collection) of the osteocalcin molecule produce stable and reproducible results.

Our bone turnover product portfolio

Resorption markers			
Analyte	**Sample material**	**ELISA**	**ChLIA ****
Alpha C-terminal telopeptides of type I collagen (αCTX-I)	Urine	AC-04F1	-
Beta C-terminal telopeptides of type I collagen (βCTX-I)	Serum, plasma	AC-02F1	IS-3000N/IS-3020N/ IS-3030N
	Urine	AC-05F1	-
C-terminal telopeptides of type I collagen (CTX-I)	Urine	AC-03F1	-
Tartrate-resistant acid phosphatase (TRAcP 5b)	Serum, plasma	SB-TR201A	IS-4100/IS-4130
Formation markers			
Analyte	**Sample material**	**ELISA**	**ChLIA ****
Bone-specific alkaline phosphatase (BAP)	Serum	AC-20F1	-
	Serum, plasma	-	IS-2800/IS-2830
N-terminal propeptide of type I procollagen (PINP), intact	Serum, plasma	-	IS-4000/IS-4030
Osteocalcin	Serum, plasma	AC-11F1	IS-2900/IS-2930

** IS-##20N are the corresponding calibrator sets; IS-##30(N) are the corresponding control sets.

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Medical conditions affecting bone remodelling

Osteoporosis is the main clinical condition impacting bone remodelling, leading to the deterioration of the integrity of the bone structure. Osteoporosis affects approximately one in three women and one in five men, and is considered a silent epidemic since bone loss itself has no symptoms. The first sign of osteoporosis is often a fracture.

Other medical conditions such as hyperparathyroidism, hyperthyroidism, lipid storage disorders, Paget's disease, nutritional rickets and osteomalacia, metastasis of the bone and medication-induced disorders also affect the bone remodelling cycle.

Circadian variation in biochemical bone resorption markers

Circadian variability has more impact on markers of bone resorption than other sources of variability. To reduce the effect of circadian rhythms on the clinical interpretation of bone resorption markers, it is essential that the timing of the sample collection is tightly controlled *(Figure 2)*. For optimal results it is recommended to draw blood as fasting morning samples.

Also for monitoring the individual patient, follow-up samples should be collected under the same conditions as the baseline sample. Bone resorption markers have a diurnal rhythm with the marker level being the highest in the morning, which is why a morning collection is usually recommended.

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